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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/817,661	03/26/2001	Jane Osbourn	84633-000100US	9792

24197 7590 07/11/2005

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EXAMINER	
EPPERSON, JON D	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 07/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/817,661	OSBOURN ET AL.	
	Examiner	Art Unit	
	Jon D. Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 April 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *2-7,15-20 and 24-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,8-14 and 21-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 March 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

1. The Response filed April 20, 2005 is acknowledged.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Status of the Claims

3. Claims 1-30 were pending. Applicants amended claim 1. No claims were added or canceled. Therefore, claims 1-30 are currently pending.

4. Claims 2-7, 15-20 and 24-30 are drawn to non-elected species and/or inventions and thus these claims remain withdrawn from further consideration by the examiner, 37 CFR 1.142(b), there being no allowable generic claim.

5. Therefore, claims 1, 8-14 and 21-23 are examined on the merits in this action.

6. The Examiner further notes that this application contains claims 15-20 and 24-30 drawn to a nonelected invention(s). This was addressed in the previous action (e.g., see 11/17/04 Non-final Action, page 2, paragraph 3). A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144). See MPEP § 821.01.

Withdrawn Objections/Rejections

7. The objection to the specification is withdrawn.

Outstanding Objections and/or Rejections

8. Claims 1, 8-14 and 21-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pluckthun et al. (WO 98/48008) (Date of Patent is **October 19, 1998**) (IDS AC) and Dubois et al. (WO 98/00547) (Date of Patent is **January 8, 1998**) (IDS BA) and Landt et al. (Landt, O.; Grunert, H.-P.; Hahn, U. "A general method for rapid site-directed mutagenesis using the polymerase chain reaction" *Gene* **1990**, *96*, 125-128).

For ***claim 1***, Pluckthun et al. (see entire document) teach ribosome display (e.g., see abstract and figure 1), which reads on steps (a)-(c) of claim 1. For example, Pluckthun et al. disclose **(a)** providing mRNA molecules that lack in-frame stop codons (e.g., see figure 1, step 1; see also page 3, last paragraph, "Accordingly, the present invention relates ... (a) translating a population of mRNA molecules devoid of stop codons"). Pluckthun et al. also disclose **(b)** incubating the mRNA molecules under conditions for ribosome translation of the mRNA molecules to produce encoded specific binding pair member, whereby complexes each comprise ribosome, mRNA and encoded specific binding pair member (e.g., see figure 1, step 2). Pluckthun et al. further disclose **(c)** bringing the complexes into contact with the complementary sbp member of interest, and selecting one or more complexes displaying specific binding pair member able to bind the complementary sbp member of interest under the conditions of the

selection (e.g., see figure 1, steps 3 and 4). Pluckthun et al. also disclose both prokaryotic and eukaryotic ribosome display systems (e.g., see bottom of page 8, "Preferably, the translation is carried out in a prokaryotic translation system ... Alternatively, the translation system may be carried out in a eukaryotic translation system").

For ***claim 8***, Pluckthun et al. teach the use of heparin (e.g., see page 11, last paragraph, "In a most preferred embodiment, said blocking compound is ... heparin. Heparin has been suggested to be included as RNase inhibitor (WO 91/05058), but it has surprisingly been found in accordance with the present invention that it additionally decreases non-specific binding").

For ***claim 11***, Pluckthun et al. teach retrieving mRNA from a complex selected in step (c) (e.g., see figure 1, step 5).

For ***claim 12***, Pluckthun et al. teach amplifying and copying the retrieved mRNA into DNA (e.g., see figure 1, step 6; see also page 9, first full paragraph, "The amplification of cDNA, preferably by PCR, with or without subsequent cloning into a suitable vector, further significantly facilitates the identification of the desired nucleic acid molecule"; see especially bottom of page 8, "In a further preferred embodiment of the method of the present invention step (d) comprises (da) reverse transcribing said mRNA; (db) optionally amplifying the resulting cDNA").

For ***claims 13 and 22***, Pluckthun et al. teach the use of *in vitro* expression systems (e.g., see page 3, last paragraph, "Accordingly, the present invention relates to a method for identifying a nucleic acid molecule encoding a

(poly)peptide that interacts with a target molecule comprising the following steps: (a) translating a population of mRNA molecules devoid of stop codons in the correct reading frame in an in vitro translation system").

For ***claims 14 and 23***, Pluckthun et al. disclose isolating and purifying the product (e.g., see figure 1, steps 4 and 5; see also example 7).

The prior art teachings of Pluckthun et al. differ from the claimed invention as follows:

For ***claim 1***, Pluckthun et al. are deficient in that they do not specifically teach the use of "encapsidation" to protect the mRNA in a viral coat protein. Pluckthun et al. only teach the use of stem-loop sequences and ribonuclease inhibitors like vanadyl ribonuclease complexes (e.g., see Pluckthun et al., example 8; see also bottom of page 7).

For ***claims 9 and 21***, Pluckthun et al. are deficient in that they do not explicitly teach the use of "mutagenic primers" in RT-PCR. Pluckthun et al. only teach the use of RT-PCR for the purposes of mutagenizing the cDNA library, but they do not state how they do it i.e., "mutagenic primers" are never mentioned (e.g., see page 4, paragraph 4, "The population of mRNA molecules may be of varying origin. For example, it may be derived from a cDNA library ... Particularly advantageous is also the use of the present invention in mutagenized (poly)peptides to find improved variants"; see also example 7, "Thus, the selective pressure to maintain antigen binding, executed by binding and elution from immobilized antigen is clearly operating, albeit in the context of an ongoing genetic diversification through PCR errors").

For ***claim 10***, Pluckthun et al. do not teach the use of tobacco mosaic virus.

However, Dubois et al. teach the following limitations that are deficient in Pluckthun et al.:

For ***claim 1***, Dubois et al. (see entire document) teach the use of in vitro encapsidation using viral coat proteins to protect labile mRNA (e.g., see Dubois et al., Summary of Invention; see also page 10, lines 17-28; see also claims 3 and 4; see also page 56, lines 19-21).

For ***claims 9 and 21***, Landt et al. teach the use of "mutagneic primers" as a "general and rapid method for site-directed mutagenesis" (e.g., see Landt et al., abstract).

For ***claim 10***, Dubois et al. teach the use of tobacco mosaic virus (e.g., see Dubois et al., claim 16).

It would have been obvious to one skilled in the art at the time the invention was made to protect the nuclease labile mRNA as taught by Pluckthun et al. in their ribosome display experiments with viral coat proteins as taught by Dubois et al. because Pluckthun et al. state that their mRNA are susceptible to nuclease digestion and Dubois et al. state that they have a method for protecting mRNA from this type of digestion via viral coat protein encapsidation (e.g., see Pluckthun et al., example 8; see also bottom of page 7 wherein stem-loops and vanadyl inhibitors are used to protect the mRNA from nuclease digestion; see also Dubois et al., abstract; see also page 10, lines 17-28; see also page 3, paragraph 2, "RNA bacteriophages have long been used as model systems to study the

mechanisms of RNA replication and translation. The RNA genome within RNA bacteriophages is resistant to ribonuclease digestion due to the protein coat of the bacteriophage"). Furthermore, one of ordinary skill in the art would have been motivated to use the viral coat protein taught by Dubois et al. to replace and/or add to the stem-loop/vanadyl inhibitor protection because Dubois et al. state, "ArmoredRNA withstands plasma/serum nucleases very well compared to naked RNA" (e.g., see page 36, second to last paragraph) and also that the viral coat proteins are easy to group and purify in many cases (e.g., see page 3, paragraph 2, "Bacteriophage are simple to grow and purify, and the genomic RNA is easy to purify from the bacteriophages"). Dubois et al. also state, "the intact RNA is easily extracted from the Armoreed RNATm standard particles (e.g., see Dubois et al., paragraph bridging pages 10-11). In addition, Dubois et al. state that "in vitro" expression is a "preferred embodiment" for their resistant recombinant RNA "ReRNA" (e.g., see Dubois et al., paragraph bridging pages 10 and 11, "The non-bacteriophage RNA may be used ... for transient gene expression in vitro"; see also page 12, lines 12-19, "In contrast, in some embodiments, the ArmoredRNA™ method is a cis method where the Coat Protein is being translated from the same RNA that is to be packaged [i.e., extraction of the RNA from the coat proteins before translation is not required]"; see also page 56, lines 19-21, "The Armored RNA™ may also be added to in vitro translation systems such as a rabbit reticulocyte extract"), which would encompass the "in vitro" expression embodiments set forth by Pluckthun et al. without the prior art limitations of partial protein synthesis inhibition (e.g., see Pluckthun et al.,

example 5, "Nucleases were found to be efficiently inhibited by vanadyl ribonucleoside complexes ... even though protein synthesis was partially inhibited"). Finally, one of ordinary skill in the art would have reasonably expected to be successful because Dubois et al. teach that their viral coat protein encapsidation method can be use for "in vitro" expression systems both in prokaryotes and eukaryotes (e.g., see Dubois et al., page 11, paragraph 1, "The non-bacteriophage RNA may be used ... for transient gene expression in vitro"), which would encompass the "in vitro" expression systems of Pluckthun. In addition, RNA capsid proteins have generally been used to encapsulate a wide variety of molecules (e.g., see Dubois et al., paragraph bridging pages 6-7) and thus the specificity for encapsidation is considered to be quite broad (i.e., generally applicable to many systems).

Furthermore, it would have been obvious to one skilled in the art at the time the invention was made to employ the "mutagenic primers" as taught by Landt et al. in the ribosome display as taught by Pluckthun et al. because a preferred embodiment of Pluckthuns' invention requires mutagenesis of the displayed polypeptide via RT-PCR and PCR error (see claims 9 and 21 above), which would encompass the mutagenic PCR techniques described by Landt et al. Furthermore, a person of skill in the art would have been motivated to use the mutagenic primers as taught by Landt et al. because Landt et al. explicitly state that their method which employs the use of said primers is "general and rapid" (e.g., see Landt et al., abstract). Finally, a person of skill in the art would have reasonably expected to be successful because Pluckthun et al. teach that

mutagenic PCR methods can be used (see above) and Landt et al. state that their method can be "generally" applied (e.g., see Landt et al., abstract).

Response

9. Applicant's arguments directed to the above 35 U.S.C. § 103(a) rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicants argue, "Dubois et al. teaches that encapsidation in the bacteriophage proteins prevents translation of the RNA ... and moreover, that prior to translation ... it is required to extract the RNA from the particles", which presumably emphasizes the non-obviousness of the present claims (e.g., see 4/20/05 response, pages 8-9; see also page 9, last paragraph, "Even if one skilled in the art would combined Pluckthun et al. and Dubois et al., it is clear that Dubois et al. teaches a requirement to dissociate RNA from viral coat before translating").

[2] Applicants argue, "The present claims are based in part on the findings reported in the application (see, for example, Example 4) that mRNA of an mRNA, ribosome and displayed protein complex can be packaged. As discussed on page 8 of the application, it was not obvious that this could be achieved. In addition, documents cited in the application, including Hwang et al. ... support the non-obviousness. In summary, there was no basis in the art for any reasonable expectation of success" (e.g., 4/20/05 response, page 9, second to last paragraph).

[3] Applicants argue that "steric exclusion" of the "ribosome" would presumably prevent encapsidation and cite Hwang et al. in support of this argument (e.g., see 4/20/05 response, page 9, last paragraph).

This is not found persuasive for the following reasons:

[1] In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., the ability to translate mRNA in the presence of bacteriophage proteins and/or particles) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Here, the claimed method does not specify at what point the viral coat proteins are "provided" to the mRNA for encapsidation. Thus, the coat protein could be provided "before" the translation step, for example before step (a), to store the mRNA that will eventually be used to make the mRNA, ribosome, and displayed specific binding member complex. Likewise, the coat protein could be provided "after" the translation step, for example after step (c), to protect the mRNA in the complex itself or at some later time when the mRNA has been purified and/or dissociated from the complex (i.e., Applicants use of "comprising" terminology does not preclude the use of additional method steps). Thus, Applicants' arguments are not commensurate in scope with the claims.

In addition, the Examiner contends that Applicants' interpretation of the Dubois et al. reference is inconsistent with the plain language of the recited passage. Applicants argue that the intact RNA must first be "extracted" from the Armored RNA™ particles before translation can occur and, as a result, the Armored RNA™ would not be suitable

for "in vitro" expression. However, Dubois et al. clearly states that "in vitro" expression is a preferred embodiment (e.g., see Dubois et al., paragraph bridging pages 10 and 11, "The non-bacteriophage RNA may be used in many applications [including] ... transient gene expression in vitro"; see also page 56, lines 19-21, "The Armored RNA™ may also be added to in vitro translation systems such as a rabbit reticulocyte extract. As stated earlier, capped, polyA mRNA may used if the reRNA is packaged post-transcription using an in vitro packaging system"). Thus, Applicants interpretation that the reRNA would not be useful for protecting mRNA from ribonuclease degradation in such "in vitro" systems is simply unjustified and not consistent with the plain language of the reference. Furthermore, the recited passage does not state that intact RNA "must" be extracted from the Armored RNA™ "before translation" can occur as alleged by Applicants. The recited passage merely states that the intact RNA "can be" easily extracted without any further reference to method steps involving translation (i.e., there is no nexus here). Furthermore, Dubois et al. recite specific embodiments of in vitro expression wherein such an extraction step was not performed (e.g., see also page 12, lines 12-19, "In contrast, in some embodiments, the ArmoredRNA™ method is a cis method where the Coat Protein is being translated from the same RNA that is to be packaged [i.e., extraction of the RNA from the coat proteins before translation is not required]").

[2] Applicant's arguments fail to comply with 37 CFR 1.111(b) because they amount to a general allegation that the claims define a patentable invention without specifically pointing out how the language of the claims patentably distinguishes them from the references. Here, Applicants never define the portions of page 8 that are being

relied upon to support their non-obvious argument, nor do they provide any rationale for how those passages would overcome the present rejection. In addition, Applicants never define and/or provide the section(s) of the Hwang et al. reference that are being relied upon to support their non-obviousness argument, nor do they provide any rationale and/or support for such assertions. Finally, Applicants never provide any support whatsoever for the assertion that there is no reasonable expectation of success. The Examiner further notes that Applicants have not provided any rationale why their claimed mRNA "of an mRNA, ribosome and displayed protein complex" would act any differently than the mRNA that was successfully encapsidated by Dubois et al. and, as a result, there would be a high expectation of success.

[3] In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., encapsidation of the ribosome) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Here, Applicants' claims merely require that the mRNA be encapsidated, not the ribosome. The word "of" in the claim element "... encapsidating mRNA of complexes of mRNA, ribosome and displayed specific binding member" can broadly be interpreted as denoting the origin of the mRNA (e.g., see Soukhanov, et al. Eds. Webster's II New Riverside University Dictionary. Boston: The Riverside Publishing Company 1988, page 815, "of ... 1. Derived or coming from"). Thus, claim 1 can be interpreted as, "... encapsidating mRNA derived or coming from complexes of mRNA, ribosome and displayed specific binding member", which does not include the

encapsidation of the ribosome. Please note that other interpretations are also possible (i.e., the word "of" has many definitions, see Webster's Dictionary). Thus, Applicants' arguments are not commensurate in scope with the claims.

Furthermore, Dubois et al. recite specific embodiments of "in vitro" expression wherein such an extraction step was not performed (e.g., see also page 12, lines 12-19, "In contrast, in some embodiments, the ArmoredRNA™ method is a cis method where the Coat Protein is being translated from the same RNA that is to be packaged [i.e., extraction of the RNA from the coat proteins before translation is not required]"). Thus, "steric exclusion" was did not preclude "in vitro" expression in these embodiments.

Accordingly, the 35 U.S.C. § 103(a) rejection cited above is hereby maintained.

Conclusion

Applicant's amendment necessitated any new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon D. Epperson, Ph.D.
July 2, 2005

BENNETT CELSA
PRIMARY EXAMINER